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10/053,530	01/17/2002	Jeffrey A. Ledbetter	30906/41458UTL2	8993
4743	7590	03/23/2007	EXAMINER	
MARSHALL, GERSTEIN & BORUN LLP 233 S. WACKER DRIVE, SUITE 6300 SEARS TOWER CHICAGO, IL 60606			BLANCHARD, DAVID J	
			ART UNIT	PAPER NUMBER
			1643	
SHORTENED STATUTORY PERIOD OF RESPONSE		MAIL DATE	DELIVERY MODE	
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Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

<b>Office Action Summary</b>	<b>Application No.</b>	<b>Applicant(s)</b>	
	10/053,530	LEDBETTER ET AL.	
	<b>Examiner</b> David J. Blanchard	<b>Art Unit</b> 1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --  
**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).

Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

#### Status

- 1) Responsive to communication(s) filed on 16 January 2007.
- 2a) This action is FINAL.                    2b) This action is non-final.
- 3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

#### Disposition of Claims

- 4) Claim(s) 16,23-44,48,102 and 142-148 is/are pending in the application.
  - 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) Claim(s) \_\_\_\_\_ is/are allowed.
- 6) Claim(s) 23-44, 48, 102-16 and 142-148 is/are rejected.
- 7) Claim(s) \_\_\_\_\_ is/are objected to.
- 8) Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

#### Application Papers

- 9) The specification is objected to by the Examiner.
- 10) The drawing(s) filed on \_\_\_\_\_ is/are: a) accepted or b) objected to by the Examiner.  
 Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
 Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

#### Priority under 35 U.S.C. § 119

- 12) Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
  - a) All    b) Some \* c) None of:
    1. Certified copies of the priority documents have been received.
    2. Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
    3. Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

#### Attachment(s)

1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892)	4) <input type="checkbox"/> Interview Summary (PTO-413)
2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)	Paper No(s)/Mail Date. _____
3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)	5) <input type="checkbox"/> Notice of Informal Patent Application
Paper No(s)/Mail Date _____	6) <input type="checkbox"/> Other: _____

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### **DETAILED ACTION**

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 16 January 2007 has been entered.
2. Claims 1-22, 45-47, 49-101 and 107-141 are cancelled.  
Claims 23-24, 35-36 and 38 have been amended.  
Claims 146--148 have been added.
3. Claims 23-44, 48, 102-106 and 142-148 are pending and under consideration.
4. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.
5. This Office Action contains New Grounds of Rejections.

### ***Withdrawn Objections/Rejections***

6. The objection to the specification in the use of trademarks is withdrawn in view of the amendments to the specification filed 12/12/2006.
7. The objection to the specification as misspelling the term "protei" is withdrawn in view of the amendment to the specification filed 12/12/2006.
8. The objection to claims 35-36 and 38 under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim is withdrawn in view of the amendments to the claims.
9. The rejection of claims 39-44, 47-48 and 142 under 35 U.S.C. 112, second paragraph, as being indefinite in the recitation "wherein said binding domain polypeptide is a single chain Fv capable of binding CD20" in claim 39 is withdrawn in view of the amendments to the claims.
10. The rejection of claims 23, 25-44, 47-48, 102-106 and 142-145 under 35 U.S.C. 112, second paragraph, as being indefinite in the recitation "wherein said hinge

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peptide is an IgG or IgA hinge peptide in which the number of cysteine residues is reduced to two, provided that when the hinge peptide contains two cysteines the first cysteine of the hinge that is responsible for forming a disulfide bond with a light chain constant region in a naturally occurring IgG or IgA antibody is not deleted or substituted..." is withdrawn in view of the amendments to the claims.

11. The rejection of claims 23 under 35 U.S.C. 102(e) as being anticipated by Gillies et al (U. S. Patent Application Publication US 2003/0044423A1, with priority to 60/274,096, 3/7/01, cited on PTO-892 mailed 8/27/04) is withdrawn in view of applicants' arguments and the amendments to the claims which require preservation of the first cysteine of the hinge that is responsible for forming a disulfide bond with a light chain.

12. The rejection of claims 23, 25-28, 31-34, 39, 142 and 143-145 under 35 U.S.C. 102(a) as being anticipated by Wu et al (Protein Engineering 14(12):1025-1033, 2001, IDS filed 6/7/04) is withdrawn in view of applicants' arguments and amendments to the claims.

### ***Priority***

The following is reiterated for convenience. The disclosure of a single specific species in prior application USSN 60/367,358 does not provide adequate written support for the myriad of other species of single chain proteins of the present claims, including those that bind to CD19, CD22, CD30 ligand, CD54, CD106, CD2, CD5, CD10, CD27, CD28, CD40, CTLA-4, 4-1BB, 4-1BB ligand, IFN-gamma, IL-4, IL-12, IL-17, IL-17 receptor, CD59, CD48, CD72, CD70, CD86/B7.2, CD40 ligand, CD43, CD83, DEC-205, VLA-4, HER1, HER2, HER3, HER4, EGFR, VEGF, VEGFR, IGF-I, IGF-II, transferrin receptor, estrogen receptor, progesterone receptor, follicle stimulating hormone receptor, retinoic acid receptor, MUC-1, NY-ESO-1, NA 17-A, Melan-A/MART-1, tyrosinase, Gp-100, MAGE, BAGE, GAGE, CTA class receptors, the HOM-MEL-40 antigen encoded by the SSX2 gene, CEA and PyLT. Further, the present claims are drawn to any IgG or an IgA hinge peptide where the priority application uses

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an IgG1 hinge and there is no disclosure in the priority document wherein the hinge peptide is an IgG or IgA in which the number of cysteine residues is reduced to one and *wherein the first cysteine of the hinge that is responsible for forming a disulfide bond with a light chain constant region in a naturally occurring IgG or IgA antibody is not deleted or substituted.* Thus, not even the presently claimed CD20 single chain proteins are adequately disclosed in a manner consistent with the first paragraph of 35 U.S.C 112. Again, prior application USSN 60/367,358 discloses the anti-CD20 2H7 scFv fused to human IgG1 hinge-CH2-CH3 as well as 2H7 scFv fused with CD154, which does not provide adequate written support the broader claims of the present application as discussed supra. Therefore, the effective filing date of the presently claimed subject matter is deemed to be that of the instant application, i.e., 1/17/2002. If applicant desires priority prior to 1/17/2002; applicant is invited to point out and provide documentary support for the priority of the instant claims. Applicant is reminded that such priority for the instant limitations requires written description and enablement under 35 U.S.C. § 112, first paragraph.

13. The rejection of claims 24-26, 31-33 and 143-145 under 35 U.S.C. 102(e) as being anticipated by Gillies et al (U. S. Patent Application Publication US 2003/0044423A1 (now US Patent 7,148,321 B2), with priority to 60/274,096, 3/7/01, cited on PTO-892 mailed 8/27/04) is maintained.

The response filed 12/12/2006 states that Gillies refers to a construct having a different structure than the presently claimed constructs. In particular, applicant points out that par. 131 refers to an Ig fusion construct having multiple valency and par. 130 defines the constructs in par. 131 as proteins that have the CH2 domain of an IgG and the CH3 and CH domains of an IgM or IgA. In contrast, amended claim 24 requires a single chain protein having an IgG CH3 region and as such Gillies does not disclose each and every element recited in amended claim 24. Applicants' arguments have been fully considered but are not fund persuasive. The examiner agrees with applicants summary of the paragraphs as pointed to, however, elsewhere in the Gillies document Gillies teaches that the fusion protein may comprise IgG3 CH2 and CH3 and an IgG1

hinge, or an IgG1 hinge, IgG2 CH2 and IgG3 CH3, or an IgA hinge with IgG CH2 and CH3 domains (see par. [0019]-[0022], [0115] and [0119]). Thus, as set forth in the previous Office Action and as discussed above, Gillies et al teach each and every element recited in amended claim 24.

Thus, the rejection of claims 24-26, 31-33 and 143-145 under 35 U.S.C. 102(e) as being anticipated by Gillies et al is maintained.

14. The rejection of claims 27-28, 34, 40-41, 44, 47 and 102-103 under 35 U.S.C. 103(a) as being unpatentable over Gillies et al (U. S. Patent Application Publication US 2003/0044423A1, with priority to 60/274,096, 3/7/01, cited on PTO-892 mailed 8/27/04) in view of Shan et al (The Journal of immunology, 162:6589-6595, 1999, IDS reference EA filed 7/12/02) and Liu et al (The Journal of Immunology, 139(10):3521-3526, 1987, IDS filed 6/7/04) is maintained.

This rejection is being maintained as being dependent upon base claim 24. The response filed 12/12/2006 states that as discussed above, Gillies neither discloses or suggests a single chain protein as recited in claim 24 and Shan describes a CD20-specific single chain antibody having a hinge, CH2 and CH3 constant regions of human IgG1 wherein the hinge contains no cysteine residues and Liu teaches the sequence of the 2H7 heavy and light chain variable regions and the chimeric antibody of Liu contains wild-type human IgG1 regions and Liu does not disclose or suggest mutating the IgG1 hinge region. Applicant argues that the teachings of Gillies in view of Shan and Liu would not have led to the single chain proteins recited in claim 24 because neither Gillies, Shan nor Liu disclose a construct having one cysteine in the hinge region and further comprising an IgG CH3 region. Applicants' arguments have been fully considered but are not found persuasive. In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). In response to applicants' argument that one of skill in

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the art would not have been led to the claimed single chain proteins having one cysteine in the hinge region and further comprising an IgG CH3 region, the test for obviousness is not whether the features of a secondary reference may be bodily incorporated into the structure of the primary reference; nor is it that the claimed invention must be expressly suggested in any one or all of the references. Rather, the test is what the combined teachings of the references would have suggested to those of ordinary skill in the art. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981). In the instant case, one of ordinary skill in the art would have been motivated to and had a reasonable expectation of success at the time the invention was made to have produced a single chain protein comprising a CD20 specific scFv comprising the 2H7 VH and Vk sequences fused to a human IgG1 or IgA single cysteine hinge joined to human IgG1 CH2 and CH3 domains for immunotherapy of B cell lymphomas in view of Gillies et al and Shan et al and Liu et al because Gillies et al teach single chain antibodies linked to an IgG1 or IgA hinge wherein one or more cysteines are mutated to non-cysteine amino acid residues (preferably serine) to promote proper assembly and improved expression and Shan et al teach a monomeric anti-CD20 scFv-IgG1 wherein the VH and VL domains are joined by a 15 amino acid linker and suggests that dimeric scFv may prove superior to the disclosed monomeric construct and Shan points out that monovalent binding and lower avidities have impeded clinical applications and Liu et al teach the VH and Vk sequences of monoclonal antibody 2H7 that specifically targets CD20 expressed on B cell lymphomas. Therefore, one of ordinary skill in the art would have been motivated at the time the invention was made to produce a 2H7-scFv-Fc comprising an IgG1 or IgA hinge comprising a single cysteine to promote proper assembly and improved expression and a dimeric 2H7-scFv-Fc may prove superior to monomeric scFv-Fc constructs and would not be limited by the lower avidities that have impeded clinical applications of monovalent antibodies. Thus, there would have been several advantages to producing a 2H7-scFv-Fc comprising an IgG1 or IgA hinge comprising a single cysteine, including an increased therapeutic index in the treatment of B cell lymphomas in patients compared to monovalent constructs. The strongest rationale for combining references is a recognition, expressly or impliedly in

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the prior art or drawn from a convincing line of reasoning based on established scientific principles or legal precedent, that some advantage or expected beneficial result would have been produced by their combination. *In re Semaker*, 702 F.2d 989, 994-95, 217 USPQ 1, 5-6 (Fed. Cir. 1983).

The examiner acknowledges applicants' assertion that the references do not predict the claimed single chain proteins would retain ADCC and/or CDC and one of ordinary skill in the art would not have a reasonable expectation of success of such activity based on the combined teachings of Gillies, Shan and Liu. As reiterated above, the combined teachings and suggestions of the cited references provide the requisite motivation, reasonable expectation of success, and teach or suggest all of the claim limitations. Products of identical chemical composition cannot have mutually exclusive properties. A chemical composition and its properties are inseparable. Therefore, if the prior art teaches the identical chemical structure, the properties applicant discloses and/or claims are necessarily present. *In re Spada* 15 USPQ2d 1655, 1658 (Fed. Cir. 1990). See MPEP 2112.01. The fact that applicant has recognized another advantage which would flow naturally from following the suggestion of the prior art cannot be the basis for patentability when the differences would otherwise be obvious. See *Ex parte Obiaya*, 227 USPQ 58, 60 (Bd. Pat. App. & Inter. 1985). See MPEP 2145(II). Further, obviousness does not require absolute predictability, however, at least some degree of predictability is required. Evidence showing there was no reasonable expectation of success may support a conclusion of nonobviousness. *In re Rinehart*, 531 F.2d 1048, 189 USPQ 143 (CCPA 1976).

Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced from the references and the rejection is maintained.

15. The rejection of claims 30, 35-36 and 38 under 35 U.S.C. 103(a) as being unpatentable over Gillies et al (U. S. Patent Application Publication US 2003/0044423A1, with priority to 60/274,096, 3/7/01, cited on PTO-892 mailed 8/27/04)

in view of Kucherlapati et al (US Patent 6,150,584, filed 10/2/96) and Gilliland et al (Tissue Antigens, 47:1-20, 1996, IDS filed 6/7/04) is maintained.

This rejection is being maintained as being dependent upon base claim 24

The response filed 12/12/2006 argues as above against Gillies as not disclosing or suggesting a single chain protein according to the present claims and neither Kucherlapati and Gilliland disclose or suggest single chain proteins having the hinge CH2 and CH3 structure recited in the present claims. Applicant also argues as above that the cited references do not predict that the single chain protein presently claimed would retain ADCC and/or CDC. This has been fully considered but is not found persuasive. The examiners' remarks above regarding the teachings of Gillies apply here as well and are incorporated by reference. As noted by Applicant Kucherlapati and Gilliland were cited as teachings single-chain antibodies to various antigens. Regarding the retention of ADCC and/or CDC function, and as discussed above products of identical chemical composition cannot have mutually exclusive properties. A chemical composition and its properties are inseparable. Therefore, if the prior art teaches the identical chemical structure, the properties applicant discloses and/or claims are necessarily present. *In re Spada* 15 USPQ2d 1655, 1658 (Fed. Cir. 1990). See MPEP 2112.01. The fact that applicant has recognized another advantage which would flow naturally from following the suggestion of the prior art cannot be the basis for patentability when the differences would otherwise be obvious. See *Ex parte Obiaya*, 227 USPQ 58, 60 (Bd. Pat. App. & Inter. 1985). See MPEP 2145(II). Further, obviousness does not require absolute predictability, however, at least some degree of predictability is required. Evidence showing there was no reasonable expectation of success may support a conclusion of nonobviousness. *In re Rinehart*, 531 F.2d 1048, 189 USPQ 143 (CCPA 1976).

Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced from the references and the rejection is maintained.

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16. The rejection of claims 48 and 104-106 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gillies et al (U. S. Patent Application Publication US 2003/0044423A1, with priority to 60/274,096, 3/7/01, cited on PTO-892 mailed 8/27/04) in view of Fell et al (The Journal of Biological Chemistry, 267(22):15552-15558, 1992) and Gilliland et al (Tissue Antigens, 47:1-20, 1996, IDS filed 6/7/04) is maintained.

This rejection is being maintained as being dependent upon base claim 24

The response filed 12/12/2006 argues as above against Gillies and Gilliland.

Applicant argues that Fell teaches a chimeric L6 antibody that comprises the mouse L6 variable regions and human IgG heavy chain constant regions and Fell neither discloses or suggests a single chain antibody specific for L6, nor a protein construct as recited in the instant claims. This has been fully considered but is not found persuasive. In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). The test for obviousness is not whether the features of a secondary reference may be bodily incorporated into the structure of the primary reference; nor is it that the claimed invention must be expressly suggested in any one or all of the references. Rather, the test is what the combined teachings of the references would have suggested to those of ordinary skill in the art. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981). In the instant case, one of ordinary skill in the art would have been motivated to and had a reasonable expectation of success at the time the invention was made to have produced a single chain protein comprising an L6 carcinoma antigen specific scFv fused to human IgG1 hinge-CH2-CH3 or comprising an IgA hinge, wherein the hinge has one cysteine for human tumor therapy in view of Gillies et al and Fell et al and Gilliland et al because Gillies et al teach single chain antibodies linked to an IgG1 or IgA hinge wherein one or more cysteines are mutated to non-cysteine amino acid residues (preferably serine) to promote proper assembly and improved expression and Fell et al teach the L6 heavy and light chain variable regions of the L6 monoclonal antibody that binds the L6 antigen present on carcinomas of the breast, colon, lung and ovary and

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Gilliand et al teach scFv-Ig fusion proteins and scFv are smaller and hence, less immunogenic than native antibody, and exhibit increased tumor penetration and localization in comparison to intact antibody or Fab fragments. Therefore, one of ordinary skill in the art would have been motivated at the time the invention was made to produce an L6 carcinoma antigen specific scFv-Ig fusion protein comprising only one hinge cysteine to promote proper assembly and improved expression and for increased tumor penetration and localization and decreased immunogenicity as taught by Gilliand (pg. 2, left column). Thus, there would be several advantages to producing a single chain protein comprising an L6 carcinoma antigen specific scFv fused to human IgG1 hinge-CH<sub>2</sub>-CH<sub>3</sub> or comprising an IgA hinge, wherein the hinge has one cysteine for human tumor therapy. Thus, it would have been *prima facie* obvious to one skilled in the art at the time the invention was made to have produced a single chain protein comprising an L6 carcinoma antigen specific scFv fused to human IgG1 hinge-CH<sub>2</sub>-CH<sub>3</sub> or comprising an IgA hinge, wherein the hinge has one cysteine for human tumor therapy in view of Gillies et al and Fell et al and Gilliand et al.

Regarding the retention of ADCC and/or CDC function, and as discussed above products of identical chemical composition cannot have mutually exclusive properties. A chemical composition and its properties are inseparable. Therefore, if the prior art teaches the identical chemical structure, the properties applicant discloses and/or claims are necessarily present. *In re Spada* 15 USPQ2d 1655, 1658 (Fed. Cir. 1990). See MPEP 2112.01. The fact that applicant has recognized another advantage which would flow naturally from following the suggestion of the prior art cannot be the basis for patentability when the differences would otherwise be obvious. See *Ex parte Obiaya*, 227 USPQ 58, 60 (Bd. Pat. App. & Inter. 1985). See MPEP 2145(II). Further, obviousness does not require absolute predictability, however, at least some degree of predictability is required. Evidence showing there was no reasonable expectation of success may support a conclusion of nonobviousness. *In re Rinehart*, 531 F.2d 1048, 189 USPQ 143 (CCPA 1976).

Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced from the references and the rejection is maintained.

### ***New Grounds of Objections/Rejections***

17. Claims 23-44, 48, 102-106 and 142-148 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claims contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

As currently presented claim 23 recites that the single chain protien comprises a binding domain polypeptide comprising an IgG or IgA hinge peptide in which the number of cysteine residues is two and the first cysteine of the hinge that is responsible for forming a disulfide bond with a light chain constant region in a naturally occurring IgG or IgA antibody is not deleted or substituted, which does not have clear written supprot in the as filed disclosure. The exclusionary proviso wherein the first cysteine of the hinge that is responsible for forming a disulfide bond with a light chain constant region in a naturally occurring IgG or IgA antibody is not deleted or substituted appears to have been added in the amendment filed 10/28/2003. The response filed 6/7/2004 states that support can be found throughout the specification, specifically at pp. 10-11, 16, 25, 29, 38, ect, ect and Figs 4, 11,1 3, 19 and 20. This has been fully considered but is not found persuaisve. The pages and figures as pointed to by applicant generically disclose mutated hinge regions containing one or two cysteine residues and the disclsoure of a scFv-IgG, in which the hinge cysteines were mutatetd to serine residues by site-directed mutagenesis and the construct in which the human hinge region was substituted with a portion of the human IgA hinge (e.g., Ex. 5, Fig. 11) and the assessment of ADCC and CDC does not provide adequate written support for the currently claimed limitations, i.e., the first cysteine of the hinge that is responsible for forming a disulfide bond with a light chain constant region in a naturally occurring IgG or IgA antibody is not deleted or

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substituted because there is insufficient guidance and direction to the subgenus of single chain proteins comprising such. Further, at pg. 29, lines 16-19 of the as filed specification it states "The Cys residue of the hinge which makes a disulfide bond with a corresponding Cys of the light chain, to hold the heavy and light chains of the native antibody molecule, can be deleted or, preferably is substituted with, e.g., a Pro residue or the like." The as filed specification, drawings and claims do not disclose a single species of a single chain polypeptide comprising a binding domain polypeptide comprising an IgG or IgA hinge peptide in which the number of cysteine residues is two and the first cysteine of the hinge that is responsible for forming a disulfide bond with a light chain constant region in a naturally occurring IgG or IgA antibody is not deleted or substituted. Applicants' reliance on a generic disclosure has not provided sufficient direction and guidance to the "features" currently claimed. It is noted that a generic or a sub-generic disclosure cannot support a species unless the species is specifically described. It cannot be said that a subgenus is necessarily described by a genus encompassing it and a species upon which it reads. See In re Smith 173 USPQ 679, 683 (CCPA 1972) and MPEP 2163.05.

Additionally, the amendment to claim 24 introduces new matter. The response filed 12/12/2006 points to pg. 12, lines 10-12, which discloses that the CH2 and CH3 constant regions are from a human immunoglobulin heavy chain, which does not provide adequate written support for the limitation of an IgG CH3 domain in combination with just any heavy chain CH2, particularly where lines 13-15 on the same pg. disclose that the CH2 and CH3 are of an isotype selected from human IgG and human IgA. The as filed disclosure as pointed to by applicant does not provide adequate written support for the use of just any CH2 region in combination with an IgG CH3 region, particularly where the CH2 and CH3 are different isotypes as presently amended.

As discussed supra, the claims now recite limitations, which were not clearly disclosed in the specification as filed, and now change the scope of the instant disclosure as filed. Such limitations recited in the presently amended claims, which did not appear in the specification, as filed, introduce new concepts and violate the description requirement of the first paragraph of 35 U.S.C 112. Applicant is required to

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provide sufficient written support for the limitations recited in the present claims in the specification or claims, as filed, or remove these limitations from the claims in response to this Office Action.

18. Claims 23-44, 48, 102-106 and 142-148 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for making and using the immunoglobulin fusion proteins that mediate ADCC with the Fc comprising CH2-CH3 domains of IgG, does not reasonably provide enablement for the genus of binding domain polypeptide-CH2-CH3 IgA fusion proteins having the property of mediating ADCC. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 1 12, first paragraph, have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988).

Wands states on page 1404, "Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in *Ex parte Forman*. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The claims are drawn to a single chain protein comprising a binding domain polypeptide comprising an immunoglobulin CH2 constant region polypeptide, a CH3 constant region polypeptide and an IgG or IgA hinge wherein the first hinge cysteine responsible for forming a disulfide bond with the light chain constant region is not substituted or deleted, or wherein the IgG or IgA hinge contains one cysteine and wherein the fusion protein binds a variety of different target antigens and promotes antibody dependent cell-mediated cytotoxicity or complement fixation or both. Thus, the claims encompass single chain proteins for promoting or mediating antibody dependent

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cell-mediated cytotoxicity or complement fixation or both, wherein the single chain protein comprises just any CH2 and CH3 regions.

The specification teaches making a 2H7 scFv fused to human IgG1 hinge, CH2 and CH3 regions, wherein the single-chain protein mediates antibody dependent cell-mediated cytotoxicity and complement fixation (see Examples). The specification does not teach the extremely large genus of single-chain proteins comprising any targeting polypeptide including single-chain antibodies that bind various cell surface antigens (e.g., claims 28-30, 35-38, 146-149) and comprising an IgG or IgA hinge wherein the first hinge cysteine responsible for forming a disulfide bond with the light chain constant region is not substituted or deleted, or wherein the IgG or IgA hinge contains one cysteine and comprising just any CH2 and CH3 domains wherein the single chain protein promotes antibody dependent cell-mediated cytotoxicity or complement fixation or both. There are no working examples of a single-chain protein comprising any targeting polypeptide including single-chain antibodies that bind various cell surface antigens (e.g., claims 28-30, 35-38, 146-149) and comprising an IgG or IgA hinge wherein the first hinge cysteine responsible for forming a disulfide bond with the light chain constant region is not substituted or deleted, or wherein the IgG or IgA hinge contains one cysteine and IgA CH2 and CH3 regions wherein the single chain protein promotes antibody dependent cell-mediated cytotoxicity or complement fixation or both. The scope of the claims must bear a reasonable correlation with the scope of enablement. See In re Fisher, 166 USPQ 19 24 (CCPA 1970).

The claims are non-enabling for mediating ADCC based on the specification and in view of Gillies et al (US Patent 7,148,321 B2), which discloses that:

"IgM and IgA do not mediate ADCC. To construct a polyvalent antibody or Ig fusion that mediates ADCC" (col. 16, lines 51-53].

Thus, in view of the art recognized lack of ADCC activity associated with the IgA Fc region, one of ordinary skill in the art could not predictably extrapolate the teachings in the specification limited to a 2H7 scFv-hulgG1 Fc region that mediates ADCC and CDC to the genus of single-chain proteins comprising just any Ch2 and CH3 domains, inclusive to domains that do not mediate ADCC and CDC.

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Therefore, in view of the broadly claimed invention, the lack of predictability in the art as evidenced by Gillies, and lack of guidance in the specification with regard to using the fusion proteins comprising IgA-CH2-CH3 domains for mediating ADCC, one of skill in the art would be required to perform undue experimentation in order to practice the claimed invention.

### ***Double Patenting***

19. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

20. Claims 23-44, 48, 102-106 and 142-148 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-53 of copending Application No.11/088,693. Although the conflicting claims are not identical, they are not patentably distinct from each other.

The instant claims are drawn to a single-chain protein comprising a binding domain polypeptide capable of binding to a target biological molecule, said binding

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domain polypeptide being joined to a hinge peptide, said hinge peptide being joined to an immunoglobulin heavy chain CH2 constant region polypeptide, said CH2 constant region polypeptide being joined to an immunoglobulin heavy chain CH3 constant region polypeptide, wherein said hinge peptide is an IgG or IgA hinge peptide wherein the first cysteine of the hinge that is responsible for forming a disulfide bond with a light chain constant region in a naturally-occurring IgG or IgA antibody is not deleted or substituted or wherein the IgG or IgA hinge peptide contains one cysteine, and wherein said single chain protein (1) is capable of binding to said target, and (2) is capable of promoting antibody dependent cell-mediated cytotoxicity or complement fixation or both and wherein the binding domain polypeptide is a single-chain antibody that binds to a variety of different cell surface antigens.

Claims 1-53 of copending Application No.11/088,693 are drawn to a pharmaceutical composition comprising a pharmaceutically acceptable carrier and a therapeutically effective amount of a single-chain protein comprising a binding domain polypeptide capable of binding to a target biological molecule, said binding domain polypeptide being joined to a hinge peptide, said hinge peptide being joined to an immunoglobulin heavy chain CH2 constant region polypeptide, said CH2 constant region polypeptide being joined to an immunoglobulin heavy chain CH3 constant region polypeptide, wherein said hinge peptide is an IgG or IgA hinge peptide wherein the first cysteine of the hinge that is responsible for forming a disulfide bond with a light chain constant region in a naturally-occurring IgG or IgA antibody is not deleted or substituted or wherein the IgG or IgA hinge peptide contains one cysteine, and wherein said single chain protein (1) is capable of binding to said target, and (2) is capable of promoting antibody dependent cell-mediated cytotoxicity or complement fixation or both and wherein the binding domain polypeptide is a single-chain antibody that binds to a variety of different cell surface antigens. Applicant is reminded that "comprising" is inclusive or open-ended and does not exclude additional, unrecited elements or method steps. See MPEP 2111.03. Thus, claims 1-53 of copending Application No.11/088,693 are drawn to a species that reads upon the claims in the instant application and are drawn to an invention that is not patentably distinct.

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This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

21. Claims 24-44, 48, 102-106 and 142-148 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-22 of copending Application No.10/207,655 in view of Shan et al (The Journal of immunology, 162:6589-6595, 1999, IDS reference EA filed 7/12/02) and Liu et al (The Journal of Immunology, 139(10):3521-3526, 1987, IDS filed 6/7/04). Although the conflicting claims are not identical, they are not patentably distinct from each other.

The instant claims have been described supra.

Claims 1-22 of copending Application No.10/207,655 are drawn to a binding domain-immunoglobulin fusion protein, comprising a binding domain polypeptide fused to a mutated human IgG1 hinge region comprising one cysteine residue, said hinge region being joined to an immunoglobulin heavy chain CH2 constant region polypeptide, said CH2 constant region polypeptide being joined to an immunoglobulin heavy chain CH3 constant region polypeptide, and wherein said binding domain-immunoglobulin fusion protein specifically binds to an antigen and promotes antibody dependent cell-mediated cytotoxicity or complement fixation or both, wherein the binding domain polypeptide comprises a light chain variable region and a heavy chain variable region and binds various different cell surface antigens. Claims 1-22 copending Application No.10/207,655 do not specifically teach wherein the binding domain polypeptide is a 2H7 scFv. This deficiency is made up for in the teachings of Shan et al and Liu et al.

Shan et al teach an anti-CD20 scFv-IgG1 wherein the VH and VL domains are joined by a 15 amino acid linker. Shan et al also teach CD20 antibodies do not internalize after cell surface binding, anti-CD20 antibodies are not shed from the cell surface and CD20 is expressed at a high density on more than 95% of all B cell lymphomas and the antigenic density of CD20 is relatively homogenous from one tumor to another (see Shan et al, pg. 6594, top left column)

Liu et al teach the VH and Vk sequences of monoclonal antibody 2H7 that specifically targets CD20 expressed on B cell lymphomas.

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The claims in the instant application are obvious variants of claims 1-22 copending Application No.10/207,655 because it would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made to produce a binding domain-immunoglobulin fusion protein, comprising a 2H7 scFv fused to a mutated human IgG1 hinge region comprising one cysteine residue, said hinge region being joined to an immunoglobulin heavy chain CH2 constant region polypeptide, said CH2 constant region polypeptide being joined to an immunoglobulin heavy chain CH3 constant region polypeptide, wherein said the 2H7 scFv-IgG promotes antibody dependent cell-mediated cytotoxicity or complement fixation or both for therapeutic benefit in lymphoma patients.

One of ordinary skill in the art would have been motivated to and had a reasonable expectation of success to produce a binding domain-immunoglobulin fusion protein, comprising a 2H7 scFv fused to a mutated human IgG1 hinge region comprising one cysteine residue, said hinge region being joined to an immunoglobulin heavy chain CH2 constant region polypeptide, said CH2 constant region polypeptide being joined to an immunoglobulin heavy chain CH3 constant region polypeptide, wherein said the 2H7 scFv-IgG promotes antibody dependent cell-mediated cytotoxicity or complement fixation or both for therapeutic benefit in lymphoma patients in view of claims 1-22 copending Application No.10/207,655 and Shan et al and Liu et al because Shan et al teach an anti-CD20 scFv-IgG1 wherein the VH and VL domains are joined by a 15 amino acid linker Liu et al teach the VH and Vk sequences of monoclonal antibody 2H7 that specifically targets CD20 expressed on B cell lymphomas and according to Shan CD20 antibodies do not internalize after cell surface binding, anti-CD20 antibodies are not shed from the cell surface and CD20 is expressed at a high density on more than 95% of all B cell lymphomas and the antigenic density of CD20 is relatively homogenous from one tumor to another. Therefore, one of ordinary skill in the art would have been motivated at the time the invention was made to modify the binding domain-immunoglobulin fusion proteins of claims 1-22 copending Application No.10/207,655 to produce a 2H7 scFv-IgG promotes antibody dependent cell-mediated cytotoxicity or complement fixation or both for therapeutic benefit in lymphoma patients

since CD20 antibodies do not internalize after cell surface binding, anti-CD20 antibodies are not shed from the cell surface and CD20 is expressed at a high density on more than 95% of all B cell lymphomas and the antigenic density of CD20 is relatively homogenous from one tumor to another. Thus, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have produced a binding domain-immunoglobulin fusion protein, comprising a 2H7 scFv fused to a mutated human IgG1 hinge region comprising one cysteine residue, said hinge region being joined to an immunoglobulin heavy chain CH2 constant region polypeptide, said CH2 constant region polypeptide being joined to an immunoglobulin heavy chain CH3 constant region polypeptide, wherein said the 2H7 scFv-IgG promotes antibody dependent cell-mediated cytotoxicity or complement fixation or both for therapeutic benefit in lymphoma patients in view of claims 1-22 copending Application No.10/207,655 and Shan et al and Liu et al.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claims 24-44, 48, 102-106 and 142-148 are directed to an invention not patentably distinct from claims 1-22 of commonly assigned copending Application No.10/207,655. Specifically, see above.

The U.S. Patent and Trademark Office normally will not institute an interference between applications or a patent and an application of common ownership (see MPEP Chapter 2300). Commonly assigned copending Application No.10/207,655, discussed above, would form the basis for a rejection of the noted claims under 35 U.S.C. 103(a) if the commonly assigned case qualifies as prior art under 35 U.S.C. 102(e), (f) or (g) and the conflicting inventions were not commonly owned at the time the invention in this application was made. In order for the examiner to resolve this issue, the assignee can, under 35 U.S.C. 103(c) and 37 CFR 1.78(c), either show that the conflicting inventions were commonly owned at the time the invention in this application was made, or name the prior inventor of the conflicting subject matter.

A showing that the inventions were commonly owned at the time the invention in this application was made will preclude a rejection under 35 U.S.C. 103(a) based upon

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the commonly assigned case as a reference under 35 U.S.C. 102(f) or (g), or 35 U.S.C. 102(e) for applications pending on or after December 10, 2004.

22. No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David J. Blanchard whose telephone number is (571) 272-0827. The examiner can normally be reached at Monday through Friday from 8:00 AM to 6:00 PM, with alternate Fridays off. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms, can be reached at (571) 272-0832.

The official fax number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

David J. Blanchard  
Patent Examiner  
Art Unit 1643

DB  
March 19, 2007

